HED NEWS

Week Ending
10/25/19
Bill Zerfas, Editor

For the Office Director

**** SENSITIVE – NOT FOR DISTRIBUTION ****

OECD Webinar on Regulatory Frameworks and Their Impacts on Top-Dose Setting in Chronic Toxicity Studies. On October 16, HED staff, Liz Mendez, Monique Perron, and Cecilia Tan, participated and presented at the second of a series of webinars sponsored by the OECD to provide an overview of regulatory frameworks in the U.S. The purpose of this series of OECD webinars is to facilitate better understanding of the regulatory frameworks in several member countries, as well as how different regulatory authorities use available data to inform their strategy for top-dose selection in chronic toxicity studies. In addition to regulatory frameworks at the Office of Pesticide Programs and the Office of Pollution Prevention and Toxics from US EPA, the presentation given by the HED staff also included overview of the type of data required and used at the US Food & Drug Administration's (FDA) Center for Drug Evaluation and Research, Center for Food Safety and Applied Nutrition, and Center for Veterinary Medicine, as well as the Occupational Safety and Health Administration (OSHA). EPA, FDA and OSHA all recommended that available exposure, toxicokinetic, toxicodynamic, mechanistic and/or other relevant data should be incorporated when designing studies and evaluating results to reduce uncertainty in human health risk assessment. When dose levels in test species greatly alter the physiology of test species, the study results are unlikely to be predictive of human health outcomes. In addition to the US, Canada also presented at this webinar and were supportive of using toxicokinetic data in the selection of top doses and design of animal toxicity studies, and modern approaches to human health risk assessment, which include those that reduce reliance on animal studies to the extent possible. (Cecilia Tan, 919-541-2542)

FMC Update on the Development of PBPK/PD Models for Dimethoate and Malathion. On October 21, FMC and Exponent representatives presented to HED and PRD scientists their most recent development of the Physiologically Based Pharmacokinetic/Pharmacodynamic (PBPK/PD) models for dimethoate and malathion. FMC developed these models to characterize rat and human PK and PD differences and to estimate inter-species data-derived extrapolation

factor and scenario-specific human points of departure with the models. FMC also collected:

- *in vitro* kinetics of dimethoate, omethoate, malathion, and malaoxon metabolism;
- *in vitro* omethoate-acetylcholinesterase and malaoxon-acetylcholinesterase bimolecular inhibition rates; and
- *in vivo* time concentration data from rats exposed to dimethoate and malathion.

These data were used to parameterize the models and evaluate their performance, and the preliminary modeling results showed reasonable agreement with observed data. FMC and OPP scientists discussed strategies to improve model fit and to simulate inhalation and dermal exposures in humans. (Cecilia Tan, 919-541-2542)

Bayer Pre-submission Discussion on Dose Selection for a New Active Ingredient. On October 22, Bayer presented to OPP and PMRA scientists an overview and data from preliminary toxicokinetic (TK) and repeated dose toxicity studies (28-day and 90-day) on a new active ingredient. The purpose of this meeting is to get input from EPA and PMRA on the use of TK and toxicodynamic (TD) approach to dose selection for the 90 day and chronic toxicology studies in rats. In addition to TK (plasma and tissue concentrations over time) and TD (organ weight, body weight, histopathology) data, Bayer also presented a physiologically based pharmacokinetic (PBPK) model developed for the active ingredient using an open source software tool, Open Systems Pharmacology Suite. This model and plasma concentration data were used to estimate a kinetically-derived maximum dose (KMD). While OPP scientists encouraged the use of TK and TD data to inform dose selection, several key questions need to be answered before an appropriate KMD can be determined and used for dose selection. Some of the recommendations provided to Bayer included identifying the mode of action, the most appropriate dose metric, the animal species that is the most relevant to humans, the toxic moiety, the most relevant adverse outcomes, and other mechanistic data for better understanding of the TK and TD of this active ingredient. (Cecilia Tan, 919-541-2542)

Meeting with Bayer to Discuss Need for a CTA for Spiromesifen. The OPP IO, HED, EFED, BEAD, and PRD met to discuss concerns for thyroid toxicity for spiromesifen. HED identified the need for a Comparative Thyroid Assay (CTA) study while preparing the draft risk assessment for spiromesifen. Additional information on the toxicity studies that may address these concerns before completing the assessment were requested. Bayer presented some suggestions for refining the assessment such that the submission of the study would not affect the overall risk conclusions, but HED noted several issues with their suggestions and provided additional information on the residential exposure assessment after the meeting. HED suggested that Bayer investigate whether potential differences in

metabolism across species may inform the human relevance of thyroid toxicity observed in dogs following spiromesifen exposure and ultimately the need for a CTA. (Christine Olinger, 703-305-5406)

EPA Meeting with Captan Task Force to Discuss Voluntary Submissions for Registration Review. On October 23, Directors and/or other representatives from the HED, PRD, the OPP IO, FEAD, and RD met with members of the Captan Task Force (CTF) to discuss EPA's technical questions, feedback, and next steps related to several voluntary data submissions. Comments, white papers, and a suite of data were submitted to EPA by the CTF during and after the public comment period for the Draft Human Health Risk Assessment of Captan to address occupational handler and post-application exposure risks. Discussion topics included both dermal (e.g., human toxicokinetic studies and modeling/dermal absorption factor information, dislodgeable foliar residue dissipation studies) and inhalation (e.g., particle size and storage stability/physical properties information and data). EPA provided additional feedback to the CTF during this discussion. Several next steps were identified, and additional white papers and/or data are expected to be submitted for HED review. Captan, Case 0120, Docket ID# EPA-HQ-OPP-2013-0296. (Laura Bacon, 703-305-7390)

Conference Call with BASF on Rotational Crop Restrictions. On October 17, 2019, members of HED/RAB I and RD met with BASF to discuss rationale in support of the inclusion of rice, cotton, and sunflower for crop rotation after treatment with the recently registered fungicide, mefentrifluconazole. HED encouraged the petitioner to prepare a position paper for presentation to ChemSAC. (George Kramer, 305-5079)

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Meeting with Diquat Dibromide Consumer Products Group. Members of HED and PRD met with the Diquat Dibromide Consumer Products Group to discuss mitigation options for diquat products sold for use by residential consumers. Diquat is an herbicide co-formulated with other active ingredients for use of weed control and turf renovation in residential areas. Mitigation options were proposed due to the increase in recent incident reports. The registrants provided information on feasible packaging and labeling revisions and their concerns with some of EPA recommendations. EPA agreed to consider the registrants' concerns moving forward with mitigation and labeling requirements for these products. (Cassi Walls, 703-308-0078)

Meeting with Chloropicrin Task Force on Amended Uses. Staff from HED, RD, PRD, and EFED met with member of the Chloropicrin Task Force (CTF) and their consultants to discuss the EPA assessment of their proposed amendments to

product labels, modifying the application equipment. The CTF discussed the EPA recommendations for buffers, including field size and the inputs of the models used to determine buffers. CTF will be submitting the supporting information for EPA consideration (Christine Olinger, 305-5406)

HED Representative Participated in the International Liaison Group on Methods for Risk Assessment of Chemicals in Food (ILMERAC) Meeting. On October 23, Evisabel Craig provided a presentation on OPP's approach to cumulative risk assessment (CRA) at the ILMERAC conference-call meeting. Overviews on CRA approaches from the OECD, WHO, EuroMix, Health Canada, US FDA, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES), and the European Food Safety Agency (EFSA) were also presented. A face to face meeting is planned for October of 2020 to discuss potential areas for harmonization. (Evisabel Craig, 703-347-0108)

Chemical	Deliverable	Branch
Difenoconazole	Human Health Risk Assessment	RAB IV
Tebuconazole	Human Health Risk Assessment	RAB III

For HED

RAB IV Welcomes Jeremy Leonard, Ph.D.
Jeremy recently completed his fellowship with the Oak Ridge Institute for Science and Education (ORISE) at the EPA location in RTP, North Carolina, while working in the National Exposure Research Laboratory under the mentorship of Cecilia Tan. His primary research focused on investigating the influence of exposure and pharmacokinetic behaviors on the interpretation of high-throughput *in vitro* toxicity results to support the development of Adverse Outcome Pathways and their use in risk assessment. Prior to this work, Jeremy received his Ph.D. in Environmental Toxicology from North Carolina State University, his M.S. in Marine Science from the University of North Carolina-Chapel Hill, and his B.S. degrees in both Biology and Interdisciplinary Studies from the University of Georgia.

RAB IV Completed a DRAFT Human Health Risk Assessment for Difenoconazole. Difenoconazole is a broad-spectrum fungicide belonging to the triazole group of fungicides proposed for amended uses to increase application use rates on golf course turfgrass, ornamentals, Christmas trees, and for a new end-use product registration. The proposed uses did not change the previously conducted dietary assessment which resulted in exposure estimates less than HED's level of concern. Aggregate, residential post-application, occupational handler, and occupational post-application exposure and risk assessments were updated and resulted in no risk estimates of concern. The proposed uses did not change the results of the aggregate assessment for the triazole metabolites which remains not of concern. The RAB IV Difenoconazole Risk Assessment Team includes: Brian Van Deusen (ORE and Risk Assessor), Bonnie Cropp-Kohlligian (Residue Chemistry), Thurston Morton (Dietary), and Minerva Mercado (Toxicology). (Brian Van Deusen, 703-347-8025)

RAB III Completed Tebuconazole Risk Assessment. On Oct 24, RAB III completed a human health risk assessment for new uses of tebuconazole. IR-4 petitioned OPP for new use and tolerance for tebuconazole on watercress, the new use of tebuconazole on greenhouse grown tomatoes, as well as several crop group updates. HED concluded that there were no dietary risks of concern or potential aggregate risks of concern. The proposed new uses did not significantly change the most recent aggregate human health risk assessment for free triazole and its conjugates, and remain below HED's level of concern. The proposed label directions associated with the watercress use did not prohibit the use of handheld mechanical sprayer which would lead to risk estimates of concern. However, OPP's Biological Economic Analysis Branch (BEAD) indicated that handheld mechanical sprayers would not be an application method for watercress, and so HED recommended that a prohibition for this application method be placed on the label for the watercress use. All other occupational risks were not of concern. (Barry O'Keefe, 703-308-8035)